Amendments to the Specification:

Please insert the Sequence Listing being filed concurrently herewith into the specification.

Please amend paragraph 68 on page 18 as shown below.

Some representative duplexed constructs amenable to the present invention are shown below:

5'-NN NNN NNN N(N)n NNN NNN NNN-3' as (SEQ ID NO.: 53)
3'-NN NNN NNN N(N)n NNN NNN NNN-5' s (SEQ ID NO.: 53)

5'-NN NNN NNN N(N)n NNN NNN NNN-3' as (SEQ ID NO.: 53)
3'-NN NNN NNN N(N)n NNN NNN NNN-5' s (SEQ ID NO.: 53)

5'-NN NNN NNN N(N)n NNN NNN NNN-3' as (SEQ ID NO.: 53)
3'-NN NNN NNN N(N)n NNN NNN NNN-5' s (SEQ ID NO.: 53)

5'-N NNN NNN N(N)n NNN NNN NNN-3' as (SEQ ID NO.: 53)
3'-N NNN NNN N(N)n NNN NNN NNN-5' s (SEQ ID NO.: 53)

5'-N NNN NNN N(N)n NNN NNN NNN-3' as (SEQ ID NO.: 53)
3'-N NNN NNN N(N)n NNN NNN NNN-5' s (SEQ ID NO.: 53)

5'-N NNN NNN N(N)n NNN NNN NNN-3' as (SEQ ID NO.: 53)
3'-N NNN NNN N(N)n NNN NNN NNN-5' s (SEQ ID NO.: 53)

Please amend paragraph 156 on page 50 as follows.

To better understand the higher RNA affinity of 2'-*O*-methoxyethyl substituted RNA and to examine the conformational properties of the 2'-*O*-methoxyethyl substituent, two dodecamer oligonucleotides were synthesized having SEQ ID NO: 54 ~~6~~ (CGC GAA UUC GCG) and SEQ ID NO: 55 ~~7~~ (GCG CUU AAG CGC). These self-complementary strands have every 2'-position modified with a 2'-O-methoxyethyl. The duplex was crystallized at a resolution of 1.7 Ångstrom and the crystal structure was determined. The conditions used for the crystallization were 2 mM oligonucleotide, 50 mM Na Hepes pH 6.2-7.5, 10.50 mM $MgCl_2$, 15% PEG 400. The crystal data showed: space group *C*2, cell constants *a*=41.2 Å,

b=34.4 Å, *c*=46.6 Å, =92.4°. The resolution was 1.7 Å at -170°C. The current *R*=factor was 20% (R_{free} 26%).

Please amend paragraph 168 on page 53 as shown below.

Molecular modeling experiments were performed to study further enhanced binding affinity of oligonucleotides having 2'-O-modifications. Computer simulations were conducted on compounds having SEQ ID NO: 54 6, r(CGC GAA UUC GCG), having 2'-O-modifications of the invention located at each of the nucleoside of the oligonucleotide. The simulations were performed with the oligonucleotide in aqueous solution using the AMBER force field method (Cornell *et al., J. Am. Chem. Soc.*, 1995, *117*, 5179-5197)(modeling software package from UCSF, San Francisco, CA). The calculations were performed on an Indigo2 SGI machine (Silicon Graphics, Mountain View, CA).

Please amend paragraph 224 on page 76 as follows.

For example, a duplex comprising an antisense oligonucleotide having the sequence CGAGAGGCGGACGGGACCG **(SEQ ID NO. 1)**and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

```
cgagaggcggacgggaccgdTdT  Antisense Strand  (SEQ ID NO. 2)
||||||||||||||||||||
dTdTgctctccgcctgccctggc   Complement Strand (SEQ ID NO. 3)
```

or could be blunt ended excluding the deoxythymidine (dT's):

```
cgagaggcggacgggaccg      Antisense Strand (SEQ ID NO. 1)
||||||||||||||||||||
gctctccgcctgccctggc      Complement Strand (SEQ ID NO. 4)
```

Please amend paragraph 268 spanning pages 89-91 as shown below.

A dose response was performed in the PTEN system to look at positional effects of alternating 2'-O-methyl constructs in asRNA and siRNA constructs.

SEQ ID NO/ISIS NO	SEQUENCES 5'-3'
8 1/335454	5'-P-UUUGUCUCUGGUCCUUACUU (P=S, antisense)
9 1/335455	5'-P-UUUGUCUCUGGUCCUUACUU (P=S, antisense)
10 1/335456	5'-P-UUUGUCUCUGGUCCUUACUU (P=O, antisense)
11 1/335457	5'-P-UUUGUCUCUGGUCCUUACUU (P=O, antisense)
12 1/303912	5'-P-UUUGUCUCUGGUCCUUACUU (P=S, antisense)
13 2/308746	AAGUAAGGACCAGAGACAAA (P=O, sense)
14 2/335452	AAGUAAGGACCAGAGACAAA (P=O, sense)
15 2/335453	AAGUAAGGACCAGAGACAAA (P=O, sense)
	Underlined = 2'-O-methyl and 5'-P- is a 5'-phosphate group.

siRNA duplexes (5',3'-sense and 3',5'-antisense)	Activity (150 nm)
13 2/308746 (S, P=O) 5'-AAGUAAGGACCAGAGACAAA-3'	14.8
12 1/303912 (AS, P=S) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	
(unmodified standard)	

siRNA duplexes (5',3'-sense and 3',5'-antisense)	Activity (150 nm)
14 2/335452 (S, P=O)5'-AAGUAAGGACCAGAGACAAA-3'	
8 1/335454 (AS, P=S) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	43.8
10 1/335456 (AS, P=O) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	41.0
9 1/335455 (AS, P=S) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	53.1
11 1/335457 (AS, P=O) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	49.7
15 2/335453 (S, P=O)5'-AAGUAAGGACCAGAGACAAA-3'	
8 1/335454 (AS, P=S) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	54.3
10 1/335456 (AS, P=O) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	50.3
9 1/335455 (AS, P=S) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	52.2
11 1/335457 (AS, P=O) 3'-UUCAUUCCUGGUCUCUGUUU-P-5'	52.8

13 2/308746 (S, P=O)	**5'-AAGUAAGGACCAGAGACAAA-3'**	
8 1/335454 (AS, P=S)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	40.0
10 1/335456 (AS, P=O)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	26.3
9 1/335455 (AS, P=S)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	56.6
11 1/335457 (AS, P=O)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	74.4

asRNA single stranded (5',3'-sense and 3',5'-antisense)		**Activity (200 nm)**
12 1/303912 (AS, P=S)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	27.9
8 1/335454 (AS, P=S)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	53.5
10 1/335456 (AS, P=O)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	93.2
9 1/335455 (AS, P=S)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	48.3
11 1/335457 (AS, P=O)	3'-UUCAUUCCUGGUCUCUGUUU-P-5'	89.6

SEQ ID NO:	**Sequence (5'-3')**
12 1	UUUGUCUCUGGUCCUUACUU
13 2	AAGUAAGGACCAGAGACAAA

Please amend paragraph 270 spanning pages 91-92 as follows.

A dose response was performed in the PTEN system to look at positional effects of alternating 2'-F constructs in asRNA constructs.

SEQ ID NO/ISIS NO	**SEQUENCE**	
13 2/308746	5'-P-AAG UAA GGA CCA GAG AC AAA-3'	(PO, S, RNA)
12 1/303912	3'-OH-UUC AUU CCU GGU CUC UGU UU-P-5'	(PS, AS, RNA)
16 2/339927	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, S, deoxy)
17 3/339923	3'-OH-UTC AUT C^{m}CU GGT CTC TGT UT-5'-P	(PO, AS, deoxy)

18 ~~2~~/339928 5'-PO-AAG UAA GGA ^{m}CCA GAG ACA AA-3' (PO, S, deoxy)
17 ~~3~~/339923 3'-OH-UTC AUT C^{m}CU GGT CTC TGT UT-5'-P (PO, AS, deoxy)

13 ~~2~~/308746 5'-PO-AAG UAA GGA CCA GAG ACA AA-3' (PO, S, RNA)
17 ~~3~~/339923 3'-OH-UTC AUT C^{m}CU GGT CTC TGT UT-5'-P (PO, AS, deoxy)

16 ~~2~~/339927 5'-PO-AAG UAA GGA CCA GAG ACA AA-3' (PO, S, deoxy)
19 ~~3~~/339924 3'-OH-UTC AUT C^{m}CU GGT CTC TGT UT-5'-P (PS, AS, deoxy)

18 ~~2~~/339928 5'-PO-AAG UAA GGA ^{m}CCA GAG ACA AA-3' (PO, S, deoxy)
19 ~~3~~/339924 3'-OH-UTC AUT C^{m}CU GGT CTC TGT UT-5'-P (PS, AS, deoxy)

13 ~~2~~/308746 5'-PO-AAG UAA GGA CCA GAG ACA AA-3' (PO, S, RNA)
19 ~~3~~/339924 3'-OH-UTC AUT C^{m}CU GGT CTC TGT UT-5'-P (PS, AS, deoxy)

Please amend paragraph 271 on page as follows.

Underlined nucleosides are 2'-F modified nucleosides, all other nucleosides are ribonucleosides (RNA) or 2'-deoxyribonucleosides (deoxy) as annotated, PO and PS are phosphodiester and phosphorothioate respectively, 5'-P is 5'-phosphate, and ^{m}C's are 5-methyl cytidines.

SEQ ID NO:	**Sequence (5'-3')**
20 ~~3~~	TUTGTCTCTGGUCCTUACTU

Please amend paragraph 275 spanning pages 93-95 as follows.

A dose response was performed in the PTEN system to look at positional effects of alternating 2'-F constructs in asRNA constructs.

SEQ ID NO/ISIS NO	**SEQUENCE**

13 2/308746 5'-P-AAG UAA GGA CCA GAG AC AAA-3' (PO, S, RNA)
12 1/303912 3'-OH-UUC AUU CCU GGU CUC UGU UU-P-5' (PS, AS, RNA)

16 2/339927 5'-PO-AAG UAA GGA CCA GAG ACA AA-3' (PO, S, deoxy)
21 4/339925 3'-OH-TU^{m}C ATU ^{m}CCT GGU ^{m}CU^{m}C UGU TU-5'-P (PO, AS, deoxy)

18 2/339928 5'-PO-AAG UAA GGA ^{m}CCA GAG ACA AA-3' (PO, S, deoxy)
21 4/339925 3'-OH-TU^{m}C ATU ^{m}CCT GGU ^{m}CU^{m}C UGU TU-5'-P (PO, AS, deoxy)

13 2/308746 5'-PO-AAG UAA GGA CCA GAG ACA AA-3' (PO, S, RNA)
21 4/339925 3'-OH-TU^{m}C ATU ^{m}CCT GGU ^{m}CU^{m}C UGU TU-5'-P (PO, AS, deoxy)

16 2/339927 5'-PO-AAG UAA GGA CCA GAG ACA AA-3' (PO, S, deoxy)
22 4/339926 3'-OH-TU^{m}C ATU ^{m}CCT GGU ^{m}CU^{m}C UGU TU-5'-P (PS, AS, deoxy)

18 2/339928 5'-PO-AAG UAA GGA ^{m}CCA GAG ACA AA-3' (PO, AS, deoxy)
21 4/339926 3'-OH-TU^{m}C ATU ^{m}CCT GGU ^{m}CU^{m}C UGU TU-5'-P (PO, S, deoxy)

13 2/308746 5'-PO-AAG UAA GGA CCA GAG ACA AA-3' (PO, S, RNA)
22 4/339926 3'-OH-TU^{m}C ATU ^{m}CCT GGU ^{m}CU^{m}C UGU TU-5'-P (PS, AS, deoxy)

Underlined nucleosides are 2'-F modified nucleosides, all other nucleosides are ribonucleosides (RNA) or 2'-deoxyribonucleosides (deoxy) as annotated, PO and PS are phosphodiester and phosphorothioate respectively, 5'-P is 5'-phosphate, and ^{m}C's are 5-methyl cytidines.

SEQ ID NO:	**Sequence (5'-3')**
23 4	UTUGUCUCUGGTCCUTACUT

Please amend paragraph 279 on page 96 as follows.

A dose response was performed in the PTEN system to look at positional effects of alternating 2'-O-Methyl/2'-F siRNA's.

SEQ ID NO/ISIS NO	SEQUENCE (Bold = 2'-F, Underlined = 2'-OCH_3)	
13 ~~2~~/308746	5'-P-AAG UAA GGA CCA GAG AC AAA-3'	(PO, S, RNA)
12 ~~1~~/303912	3'-OH-UUC AUU CCU GGU CUC UGU UU-P-5'	(PS, AS, RNA)
24 ~~2~~/340573	5'-PO-**A**A**G** U**A**A **G**G**A** C**C**A **G**A**G** A**C**A **A**A-3'	(PO, S)
25 ~~1~~/340569	3'-OH-U**U**C **A**U**U** C**C**U **G**G**U** C**U**C **U**G**U** U**U**-5'-P	(PO, AS)
26 ~~2~~/340574	5'-PO- A**A**G **U**A**A** G**G**A **C**C**A** G**A**G **A**C**A** A**A**-3'	(PO, S)
25 ~~1~~/340569	3'-OH-U**U**C **A**U**U** C**C**U **G**G**U** C**U**C **U**G**U** U**U**-5'-P	(PO, AS)
13 ~~2~~/308746	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, AS, RNA)
25 ~~1~~/340569	3'-OH-U**U**C **A**U**U** C**C**U **G**G**U** C**U**C **U**G**U** U**U**-5'-P	(PO, AS)
24 ~~2~~/340573	5'-PO-**A**A**G** U**A**A **G**G**A** C**C**A **G**A**G** A**C**A **A**A-3'	(PO, S)
27 ~~1~~/340570	3'-OH-U**U**C **A**U**U** C**C**U **G**G**U** C**U**C **U**G**U** U**U**-5'-P	(PS, AS)
26 ~~2~~/340574	5'-PO- A**A**G **U**A**A** G**G**A **C**C**A** G**A**G **A**C**A** A**A**-3'	(PO, S)
27 ~~1~~/340570	3'-OH-U**U**C **A**U**U** C**C**U **G**G**U** C**U**C **U**G**U** U**U**-5'-P	(PS, AS)
13 ~~2~~/308746	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, AS, RNA)
27 ~~1~~/340570	3'-OH-U**U**C **A**U**U** C**C**U **G**G**U** C**U**C **U**G**U** U**U**-5'-P	(PS, AS)

Please amend paragraph 280 on page 96 as shown below.

Underlined nucleosides are 2'-OCH_3 ~~2'-F~~ modified nucleosides, bold are 2'-F modified nucleosides, PO and PS are phosphodiester and phosphorothioate respectively, 5'-P is 5'-phosphate, and ^{m}C's are 5-methyl cytidines.

Please amend paragraph 284 on page 98 as follows.

A dose response was performed in the PTEN system to look at positional effects of alternating 2'-O-Methyl/2'-F siRNA's.

SEQ ID NO/ISIS NO	**SEQUENCE (Bold = 2'-F, Underlined = 2'-OCH_3)**	
13 ~~2~~/308746	5'-P-AAG UAA GGA CCA GAG AC AAA-3'	(PO, S, RNA)
12 ~~1~~/303912	3'-OH-UUC AUU CCU GGU CUC UGU UU-P-5'	(PS, AS, RNA)
24 ~~2~~/340573	5'-PO-**AAG UAA GGA CCA GAG ACA AA**-3'	(PO, S)
28 ~~1~~/340571	3'-OH-**UUC AUU CCU GGUC UGU UU**-5'-P	(PO, AS)
26 ~~2~~/340574	5'-PO- **AAG UAA GGA CCA GAG ACA AA**-3'	(PO, S)
28 ~~1~~/340571	3'-OH-**UUC AUU CCU GGUC UGU UU**-5'-P	(PO, AS)
13 ~~2~~/308746	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, AS, RNA)
28 ~~1~~/340571	3'-OH-**UUC AUU CCU GGUC UGU UU**-5'-P	(PO, AS)
24 ~~2~~/340573	5'-PO-**AAG UAA GGA CCA GAG ACA AA**-3'	(PO, S)
29 ~~1~~/340572	3'-OH-**UUC AUU CCU GGUC UGU UU**-5'-P	(PS, AS)
26 ~~2~~/340574	5'-PO- **AAG UAA GGA CCA GAG ACA AA**-3'	(PO, S)
29 ~~1~~/340572	3'-OH-**UUC AUU CCU GGUC UGU UU**-5'-P	(PS, AS)
13 ~~2~~/308746	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, AS, RNA)
29 ~~1~~/340572	3'-OH-**UUC AUU CCU GGUC UGU UU**-5'-P	(PS, AS)

Please amend paragraph 289 on page 100 as shown below.

A number of double stranded constructs were also assayed in HeLa cells. The constructs and activities are shown below:

SEQ ID NO/ISIS NO	SEQUENCES 5'-3'	
12 1/303912	5'-PO-UU UGU CUC UGG UCC UUA CUU-3'	(AS, PS)
13 2/308746	5'-PO-AAG TAA GGA CCA GAG ACA AA-3'	(S, PO)
14 2/335452	5'-PO-AAG TAA GGA CCA GAG ACA AA-3'	(PO, 2'-OMe)
15 2/335453	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, 2'-OMe)
8 1/335454	5'-PO-UU UGU CUC UGG UCC UUA CUU-3'	(PS, 2'-OMe)
9 1/335455	5'-PO-UU UGU CUC UGG UCC UUA CUU-3'	(PS, 2'-OMe)
10 1/335456	5'-PO-UU UGU CUC UGG UCC UUA CUU-3'	(PO, 2'-OMe)
11 1/335457	5'-PO-UU UGU CUC UGG UCC UUA CUU-3'3'	(PO, 2'-OMe)
17 3/339923	5'-PO-TU TGT CTC TGG U^{m}CC TUA CTU-3'	(PO, 2'-F/2'-H)
19 3/339924	5'-PO-TU TGT CTC TGG U^{m}CC TUA CTU-3'	(PS, 2'-F/2'-H)
21 4/339925	5'-PO-UT UGU ^{m}CU^{m}C UGG TC^{m}C UTA ^{m}CUT-3'	(PO, 2'-F/2'-H)
22 4/339926	5'-PO-UT UGU ^{m}CU^{m}C UGG TC^{m}C UTA ^{m}CUT-3'	(PS, 2'-F/2'-H)
16 2/339927	5'-PO-AAG TAA GGA ^{m}CCA GAG ACA AA-3'	(PS, 2'-F/2'-H)
18 2/339928	5'-PO-AAG UAA GGA C^{m}CA GAG A^{m}CA AA-3'	(PO, 2'-F/2'-H)
25 1/340569	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PO, 2'-F/2'-OMe)
27 1/340570	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PS, 2'-F/2'-OMe)
28 1/340571	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PO, 2'-F/2'-OMe)
29 1/340572	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PS, 2'-F/2'-OMe)
24 1/340573	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, 2'-F/2'-OMe)
26 2/340574	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, 2'-F/2'-OMe)
30 1/344217	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PO, 2'-F)
31 1/344218	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PS, 2'-F)
32 1/344219	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PO, 2'-F)
33 1/344220	5'-PO-UUU GUC UCU GGU CCU UAC UU-3'	(PS, 2'-F)
34 2/344221	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, 2'-F)
35 2/344222	5'-PO-AAG UAA GGA CCA GAG ACA AA-3'	(PO, 2'-F)

Please amend paragraph 290 on page 102 as shown below.

A wide variety of additional alternating constructs have been prepared and screening in various assays is ongoing. Some representative constructs that have been made are shown below:

SEQ ID NO/ISIS NO	ANTISENSE SEQUENCES 5'-3'
36 ~~5~~/335197	5'-P-TTTGTCTCTGGTCCTTACTT-OH (AS, PS)
37 ~~5~~/335198	5'-P-TTTGTCTCTGGTCCTTACTT-OH (AS, PS)
38 ~~5~~/335201	5'-P-TTTGTCTCTGGTCCTTACTT-OH (AS, PO)
39 ~~5~~/335202	5'-P-TTTGTCTCTGGTCCTTACTT-OH (AS, PO)
40 4/335215	5'-P-UTUGUCUCUGGTCCUTACUT-OH (AS, PS)
41 ~~3~~/335216	5'-P-TUTGTCTCTGGUCCTUACTU-OH (AS, PS)
42 4/335219	5'-P-UTUGUCUCUGGTCCUTACUT-OH (AS, PO)
43 ~~3~~/335220	5'-P-TUTGTCTCTGGUCCTUACTU-OH (AS, PO)
44 ~~2~~/xxxxx	5'-P-AAGUAAGGACCAGAGACAAA-3' (S, PO)
45 ~~2~~/xxxxx	5'-P-AAGUAAGGACCAGAGACAAA-3' (S, PO)

Please amend paragraph 292 spanning pages 102-103 as shown below.

Each of the antisense strands were duplexed with each of the sense strands to give 16 different siRNA constructs.

46 ~~6~~/335211	5'-P-UTUGUCUCUGGTCCUTACUT-OH (PS)
47 ~~7~~/335212	5'-P-TUTGTCTCTGGUCCTUACTU-OH (PS)
48 ~~6~~/335213	5'-P-UTUGUCUCUGGTCCUTACUT-OH (PO)
49 ~~7~~/335214	5'-P-TUTGTCTCTGGUCCTUACTU-OH (PO)
44 ~~9~~/xxxxx	5'-P-AAGUAAGGACCAGAGACAAA-3' (S, PO)
45 ~~9~~/xxxxx	5'-P-AAGUAAGGACCAGAGACAAA-3' (S, PO)

Please amend paragraph 294 on page 103 as follows.

Each of the antisense strands were duplexed with each of the sense strands to give 8 different siRNA constructs.

50 ~~8~~/335217	5'-P-**UUUGUCUCUGGUCCUUACUU**-OH (PS)
50 ~~8~~/335218	5'-P-**UUUGUCUCUGGUCCUUACUU**-OH (PS)
51 ~~8~~/335221	5'-P-**UUUGUCUCUGGUCCUUACUU**-OH (PO)
51 ~~8~~/335222	5'-P-**UUUGUCUCUGGUCCUUACUU**-OH (PO)
36 ~~5~~/335199	5'-P-**TTTGTCTCTGGTCCTTACTT**-OH (PS)
37 ~~5~~/335200	5'-P-**TTTGTCTCTGGTCCTTACTT**-OH (PS)
38 ~~5~~/335203	5'-P-**TTTGTCTCTGGTCCTTACTT**-OH (PO)
39 ~~5~~/335204	5'-P-**TTTGTCTCTGGTCCTTACTT**-OH (PO)
44 ~~9~~/xxxxx	5'-P-**AAGUAAGGACCAGAGACAAA**-3' (S, PO)
44 ~~9~~/xxxxx	5'-P-**AAGUAAGGACCAGAGACAAA**-3' (S, PO)

Please amend paragraph 296 on page 103 as shown below.

Each of the antisense strands were duplexed with each of the sense strands to give 16 different siRNA constructs.

SEQ ID NO:	**Sequence (5'-3')**
52 ~~5~~	TTTGTCTCTGGTCCTTACTT
23 ~~4~~	UTUGUCUCUGGTCCUTACUT
20 ~~3~~	TUTGTCTCTGGUCCTUACTU
12 ~~1~~	UUUGUCUCUGGUCCUUACUU
13 ~~2~~	AAGUAAGGACCAGAGACAAA.

Please amend paragraph 324 on page 110 as follows.

For example, a duplex comprising an antisense strand having the sequence CGAGAGGCGGACGGGACCG **(SEQ ID. NO. 1)** and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

```
cgagaggcggacgggaccgTT    Antisense
||||||||||||||||||||    Strand (SEQ ID. NO. 2)
TTgctctccgcctgccctggc    Complement
                         Strand (SEQ ID. NO. 3)
```

Please amend paragraph 339 on page 114 as follows.

The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. For human cells the positive control oligonucleotide is selected from either ISIS 13920 (TCCGTCATCGCTCCTCAGGG, SEQ ID NO: 5 ~~8~~) which is targeted to human H-ras, or ISIS 18078, (GTGCGCGCGAGCCCGAAATC, SEQ ID NO: 6 ~~9~~) which is targeted to human Jun-N-terminal kinase-2 (JNK2). Both controls are 2'-O-methoxyethyl gapmers (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone. For mouse or rat cells the positive control oligonucleotide is ISIS 15770, ATGCATTCTGCCCCCAAGGA, SEQ ID NO: 7 ~~10~~, a 2'-O-methoxyethyl gapmer (2'-O-methoxyethyls shown in bold) with a phosphorothioate backbone which is targeted to both mouse and rat c-raf. The concentration of positive control oligonucleotide that results in 80% inhibition of c-H-ras (for ISIS 13920), JNK2 (for ISIS 18078) or c-raf (for ISIS 15770) mRNA is then utilized as the screening concentration for new oligonucleotides in subsequent experiments for that cell line. If 80% inhibition is not achieved, the lowest concentration of positive control oligonucleotide that results in 60% inhibition of c-H-ras, JNK2 or c-raf mRNA is then utilized as the oligonucleotide screening concentration in subsequent experiments for that cell line. If 60% inhibition is not achieved, that particular cell line is deemed as unsuitable for oligonucleotide transfection experiments. The concentrations of antisense oligonucleotides used herein are from 50 nM to 300 nM.